UNIVERSIDADE ESTADUAL DE LONDRINA

JOEL MOTTA JUNIOR

AVALIAÇÃO DA BIOCOMPATIBILIDADE, TOPOGRAFIA SUPERFICIAL E DENSIDADE RADIOGRÁFICA DE DOIS TIPOS DE POLIETILENO POROSO DE ALTA DENSIDADE.

Londrina
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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Estadual de Londrina – UEL, para obtenção do título de Mestre em Odontologia, na área de Clínica Odontológica.

Orientador: Prof. Dr. Glaykon Alex Vitti Stabile

Este exemplar corresponde à versão final da Dissertação defendida pelo aluno, e orientada pela Prof. Dr. Glaykon Alex Vitti Stabile.

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CENTRO CENTRO DE CIÊNCIAS DA SAÚDE
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ATA DE DEFESA DE DISSERTAÇÃO

Aos 11 dias do mês de dezembro do ano de 2012, na sala 590 do Centro De Ciências Da Saúde, desta Universidade, às 14:00 horas, reuniu-se a Banca Examinadora homologada pelo Programa de Pós-Graduação em Odontologia, composta por Dr.Glaykon Alex Vitti Stabile, Dr. Alexander Tadeu Sverzut e Dr. Hedelson Odenir Iecher Borges. A reunião teve por objetivo julgar o trabalho do estudante JOEL MOTTA JUNIOR sob o título: "AVALIAÇÃO DA BIOCOMPATIBILIDADE DE UM POLIETILENO POROSO DE ALTA DENSIDADE DE FABRICAÇÃO NACIONAL". Os trabalhos foram abertos pelo professor Dr. Glaykon Alex Vitti Stabile. A seguir, foi dada a palavra ao estudante para apresentação do trabalho. Cada examinador arguiu o Mestrando, com tempos iguais de arguição e resposta. Terminadas as arguições, procedeu-se ao julgamento do trabalho, concluindo a Banca Examinadora por sua APROVAÇÃO. Nada mais havendo a tratar, foi lavrada a presente ata, que vai assinada pelos membros da Banca Examinadora.

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DEDICATÓRIA

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“Nunca ande pelo caminho traçado, pois ele conduz somente até onde os outros foram.”

Alexander Graham Bell

MOTTA JÚNIOR, Joel. **Avaliação da biocompatibilidade, topografia superficial e densidade radiográfica de dois tipos de polietileno poroso de alta densidade.** 53 f. 2012. Dissertação (Mestrado em Odontologia) – Universidade Estadual de Londrina, Londrina, 2012.

RESUMO

Esta dissertação foi dividida em dois capítulos. O **Capítulo 1** avaliou a morfologia superficial (*in vitro*) e a densidade radiográfica (*in vivo*) de dois tipos de implantes de polietileno poroso de alta densidade (PPAD): o primeiro tipo, composto apenas por grânulos de polietileno foi denominado padrão (PPADp); e o segundo tipo foi uma versão do primeiro modificado por meio da adição de um marcador radiográfico radiopaco, o óxido de bismuto a 7% (PPADmr). A partir de lâminas padronizadas de PPADp e PPADmr com medidas de 40x50x2mm fornecidas pelo fabricante, foram confeccionados 90 corpos de provas cilíndricos (45 PPADp e 45 PPADmr), medindo 4,5mm de diâmetro por 2mm de altura, sendo estes submetidos à esterilização por meio de óxido de etileno. Para avaliação da morfologia topográfica *in vitro* foram selecionados aleatoriamente 5 corpos de prova de cada tipo de PPAD os quais foram submetidos a microscopia eletrônica de varredura (MEV) para análise superficial descritiva e mensuração dos espaços inter-grânulos (poros). Os dois tipos de PPAD apresentaram estruturas semelhantes entre si com relação ao tamanho e distribuição dos poros aleatoriamente; ainda foi demonstrada a presença dos cristais de óxido de bismuto no PPADmr, onde estes se apresentavam distribuídos uniformemente sobre a superfície dos corpos de prova. Os valores de distância mínima entre poros do PPADp e PPADmr foram de 136,4µm e 144,2µm respectivamente. Para mensuração da densidade radiográfica dos PPAD, foram empregados 20 coelhos, adultos, machos, da raça Nova Zelândia que foram submetidos à implantação de 4 corpos de prova em cada animal, sendo 2 implantes em defeitos ósseos criados na calota craniana (1 PPADp e 1 PPADmr) e 2 implantes em o tendão do músculo flexor digital superficial das patas posteriores (1 PPADp e 1 PPADmr). Os animais foram divididos em 4 grupos de 5 animais cada, diferindo entre sí o período ao qual os animais foram mortos (7, 14, 45 e 90 dias pós-operatórios), uma vez que cada animal recebeu ao mesmo tempo o PPADp e o PPADmr nos respectivos sítios cirúrgicos. Após a morte dos animais, as peças anatômicas foram removidas e os valores de unidade Hounsfield (UH) foram obtidos empregando-se tomografia computadorizada do tipo *Fan Beam*. Os valores resultantes foram submetidos aos testes estatísticos de Anova para um e dois fatores, onde o PPADmr mostrou redução dos valores de UH conforme os períodos analisados, sendo esta diferença entre períodos estatisticamente significante. Já o PPADp mostrou-se constante quanto ao valor de UH, exceto entre o período de 14 e 90 dias que apresentou diferenças estatísticas. Conforme as análises, o PPADrm mostrou-se eficiente na identificação ao exame tomográfico, porém instável quanto à manutenção de sua radiopacidade. O **Capítulo 2** avaliou histologicamente a biocompatibilidade do PPADp e do PPADmr inseridos em tendão do músculo flexor digital superficial (1 PPADp e 1 PPADmr) e calota craniana (1 PPADp e 1 PPADmr) de 20 coelhos machos, adultos, da raça Nova Zelândia. Foram inseridos implantes de PPADp e de PPADmr perfazendo o total de 40 amostras de cada PPAD. Os animais foram mortos em número de 5 aos períodos de 7, 14, 45 e 90 dias pós operatórios, para remoção das amostras e análise histológica. Ambos os implantes de PPAD apresentaram infiltração de tecido conjuntivo e presença de vasos sanguíneos nas amostras de calota craniana e do tendão nos períodos iniciais (7 e 14 dias). No período de 45 dias o infiltrado celular apresentou-se mais maduro com presença de fibrócitos, fibras colágenas e vasos sanguíneos; ainda neste período, no PPADmr, foram visualizados cristais do marcador radiopaco infiltrados no espaço interporos e no tecido adjacente. No período de 90 dias, o infiltrado celular mostrou-se maduro com fibrovascularização bem definida em ambos os PPAD tanto em tendão quanto em calota. Os PPAD inseridos em calota apresentaram, nos espaços interglobulares, presença de ilhas ósseas e tecido cartilaginoso. Com base na metodologia empregada, conclui-se que os dois tipos de PPAD mostraram biocompatíveis, porém com relação ao grupo do PPADmr, em virtude do desprendimento dos cristais, mais estudos devem ser feitos para compreender por que ocorre o desprendimento do marcador radiopaco dos implantes e quais as implicações clínicas deste evento.

Palavras-chave: Polietileno. Tomografia computadorizada. Fotomicrografia. Microscopia eletrônica de varredura. Teste de biocompatibilidade. Próteses e implantes. Tecido conjuntivo. Tecido ósseo.

MOTTA JÚNIOR, Joel . **Biocompatibility evaluation, and surface topography radiographic density of two types of porous polyethylene high density.** 53 f. 2012. Dissertation (Master's degree in Dentistry) – Universidade Estadual de Londrina, Londrina, 2012.

ABSTRACT

This study was divided into two chapters. The **Chapter 1** evaluated two new high-density porous polyethylene (HDPP): one standard (sHDPP) and other modified with bismuth oxide in 7% concentration (rmHDPP), by scanning electron microscopy (SEM) for microstructural evaluation and measure of the distances between pores and radiographic density using the Hounsfield Unit (HU). Were used sheets of the sHDPP and rmHDPP measuring 40x50x2 mm to create 90 circular specimens of 4.5X2 mm that were prepared in disk shape (45 sHDPP and 45 rmHDPP) and sterilized by ethylene oxide. To analyze by SEM were choose randomly five specimens of each HDPP that were analyzed descriptively their structural differences and distances between pores. The analysis revealed that the minimum space between pores in sHDPP and rmHDPP was 136.4 and 144.2µm respectively. The morphological configuration appeared similar in sHDPP and rmHDPP, except for the presence of crystals present in rmHDPP which appeared evenly distributed over the surface. To assessment of the HU, were used 20 rabbits, adults, male, New Zealand that were underwent surgical procedure to insert 4 specimens of the HDPP, 2 in calvarium (1 sHDPP and 1 rmHDPP) and 2 in tendon of the legs (1 sHDPP and 1 rmHDPP). All animals were divided into 4 groups with 5 rabbits each, these were separated conform the days of the dead (7, 14, 45 and 90 days). The exams by radiographic density were performed and the HDPP was analyzed for HU, having values analyzed to ANOVA statistical tests for 1 and 2 factors. The rmHDPP showed a decrease in HU in all periods and these values were statistically different from each other, whereas the sHDPP was constant as the value of HU, except between second and fourth periods, was statistically difference. According to these analyses is concluded that the rmHDPP was efficient to identify the CT scan, but unstable as the maintenance of its density. The **Chapter 2** analyzed the biocompatibility of two new HDPP (standard and radiopaque marker) inserted into tendon and bone rabbits using descriptive histological by coloring hematoxylin-eosin for optical microscopy analysis. Were used 20 rabbits, adults, male, New Zealand that were underwent surgical procedure to insert 4 specimens, 2 in calvarium (1 sHDPP and 1 rmHDPP) and 2 in tendon of the legs (1 sHDPP and 1 rmHDPP). All animals were divided into 4 groups with 5 rabbits each, these were separated conform the days of the dead (7, 14, 45 and 90 days). The animals were killed to obtain material for analysis. Both HDPP presented connective tissue infiltration and presence of blood vessels when inserted into the bone and tendon in earlier periods (7 and 14 days). In the period of 45 days the cellular infiltration appeared more mature with the presence of fibrocytes, collagen fibers and blood vessel in this period; when the rmHDPP, the crystal of the bismuth was found in supernatant detached from HDPP. In 90 days, both HDPP showed fibrovascularization with well-defined mature cell infiltration and the presence of bone islands at the intergranular spaces. With the analyzed material is concluded that this two HDPP proved biocompatible with the recipient tissue, but conform the rmHDPP shown detachment of the crystals, more study should be done to know about this problem and what clinical consequence.

Keywords: Polyethylene. Computed tomography. Photomicrograph. Scanning electron microscopy. Materials testing. Prostheses and implants. Connective tissue. Bone.

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INTRODUÇÃO

Os pré-requisitos básicos de todo implante utilizado na área da saúde são biocompatibilidade e a mínima citotoxidade do material, sendo então denominados quando da apresentação destas características de biomateriais ou implantes bioativos (Wellisz *et al.,* 1992; Vendemia *et al.,* 2011). Outras características fundamentais destes materiais ainda são: serem passíveis de esterilização, possuírem estabilidade dimensional e propriedades mecânicas compatíveis com seu uso, tornando-os o mais semelhante possível ao tecido no qual estão sendo empregados como substituto.

O polietileno é um polímero derivado do gás etileno composto basicamente de átomos de carbono e hidrogênio. Foi inicialmente empregado na indústria na década de 1950 na forma de polietileno de alta densidade como matéria prima para filtros, revestimentos de compartimentos de transporte e também para protetores em tapumes de portos. Seu uso na área da saúde teve início na década de 1960 na confecção de próteses articulares devido as suas propriedades de não ser absorvível e apresentar-se inerte quimicamente. O polietileno poroso de alta densidade (PPAD), outra variação do polietileno, como o próprio nome descreve, apresenta microporos em sua estrutura permitindo a migração celular e neoformação vascular em seu interior, proporcionando a este material estabilidade no sítio receptor (Friedman 2002; Coskun *et al.,* 2008), bem como o baixo potencial de risco de infecção (Merritt *et al.,* 1979). O PPAD está disponível comercialmente para uso como implantes em diversos tamanhos e formatos, tendo como características ser facilmente adaptável e bem tolerado pelos tecidos (Uysal *et al.,* 2006). Além das características de biocompatibilidade, quando comparado aos enxertos autógenos, não apresenta necessidade de área doadora levando a uma menor morbidade, possui maior facilidade de escultura e adaptação ao leito receptor, características que levam a uma redução do tempo operatório, além de ser estável dimensionalmente ao logo do tempo (Liu *et al.,* 2004; Romo & Pearson, 2008; Lin *et al.,* 2012).

Por apresentar morfologia porosa, cujos poros podem variar entre 125-250 µm (Wellisz *et al.,* 1995), o PPAD favorece o crescimento celular interno e externo de tecido conjuntivo e vasos sanguíneos em um período de 3 a 4 semanas pós-implantação, promovendo uma interface que ancora o implante ao sítio receptor (Spector *et al*., 1975; Couldwell *et al.,* 1994). Além disso, alguns autores listam como outra vantagem do PPAD ser radiolúcido, não contribuindo com a formação de artefatos em exames de imagem (Couldwell *et al.,* 1997), embora esta característica seja controversa, pois também dificulta a identificação do posicionamento do material com precisão em exames de imagem pós-operatórios (De Potter *et al.,* 2000; Coskun *et al.,* 2008; Vendemia *et al.,* 2011). As características citadas e os diversos trabalhos publicados há mais de 25 anos nas diferentes especialidades da área da saúde trazem ao PPAD a confiabilidade para a indicação clínica destes implantes na substituição de estruturas perdidas (Couldwell *et al.,* 1994; Terino, 2002; Zimm & Binder, 2010; Wang *et al*., 2012).

Por ser de fácil manuseio e eficaz em suas aplicações, o PPAD tem tido papel importante como substituto ósseo e/ou cartilaginoso para reconstrução de estruturas anatômicas em cirurgias de cranioplastia, reparo craniofacial e reconstrução de base de crânio (Liu *et al.,* 2004). Devido as suas características de biocompatibilidade, auxilia o fechamento primário do sítio cirúrgico, diminui o espaço morto e pode recobrir toda a extensão do crânio se necessário (Couldwell *et al.,* 1994; Couldwell *et al.,* 1997; Janecka, 2000; Wang *et al.,* 2012; Lin *et al.,* 2012). Já em cirurgias ortopédicas, o PPAD está presente em associação com polietileno de alto peso molecular em componentes articulares, como na utilização articulações protéticas de joelho e fêmur (Nakashima *et al.,* 2012; Naziri *et al.,* 2012). Em cirurgia oftálmica, o PPAD é indicado para o reestabelecimento do volume orbitário perdido após cirurgia de enucleação ocular (Chalasani *et al.,* 2007; Chuo *et al.,* 2009).

Em Odontologia, na especialidade de Cirurgia e Traumatologia Buco-Maxilo-Facial, o PPAD é utilizado em diversas situações onde há necessidade de substituição ou reposição de tecido ósseo ou cartilaginoso (Menderes *et al.,* 2004), tais como fraturas de assoalhos orbitários (Colombo, 2011), fraturas de ossos zigomáticos (Zimm & Binder, 2010), ossos nasais (Terino, 2002; Romo & Pearson, 2008; Reiffel *et al*., 2011), osso frontal (Kucukyuruk *et al.,* 2010), reposição de cartilagens alares e pavilhão auricular (Romo *et al.,* 2006) e ainda em indicações estéticas de preenchimento, como aumento do mento e da projeção zigomática (Friedman, 2002; Terino, 2002; Vendemia *et al*., 2011).

O PPAD é passível de escultura manual pelo cirurgião por meio de lâmina de bisturi, bem como pode ser dobrado e melhor adaptado ao ser imerso em solução salina estéril próxima a 60°C, sendo que após a sua conformação, este mantem a forma aplicada com o retorno à temperatura ambiente (Wang *et al.,* 2012). Apesar da relativa facilidade na manipulação deste material, ele apresenta algumas desvantagens como a necessidade de grande manipulação dos tecidos do leito receptor; ser susceptível a infecção quando exposto ao meio externo assim como maior dificuldade de remoção após a fibrovascularização (Boriani *et al.,* 2005).

Apesar de o PPAD ser um material já bastante estudado e aceito como implante para recontorno, preenchimento e sustentação nas suas diversas indicações (de Meijer *et al.,* 2003; Gasparini *et al.,* 2003; Renzi *et al.,* 2004; Boriani *et al.,* 2005), sua elevada tecnologia de produção associada à limitada quantidade de empresas que o produzem comercialmente, sem similar atualmente produzido em território nacional, tornam o seu custo final elevado, diminuindo assim sua aplicabilidade clínica.

Diante deste cenário, uma empresa local com experiência na manipulação e produção de PPAD para fins não médicos solicitou apoio dos autores para o desenvolvimento de implantes de polietileno poroso de alta densidade padrão (PPADp), os quais após desenvolvimento inicial tornaram-se objetos deste estudo. Ainda, no intuito de promover um diferencial quando comparado ao PPAD já disponível comercialmente, foi desenvolvido um PPAD acrescido de marcador radiopaco (PPADmr), tornando-o passível de identificação nos exames de imagens radiográficos, sem contudo desenvolver artefatos, principalmente ao empregar tomografia computadorizada. Testes preliminares *in vitro* demonstraram que as características físicas e mecânicas obtidas nos dois tipos de PPAD foram aceitáveis para sua aplicação clínica. Agora, por meio de novos testes *in vitro* e *in vivo* investiga-se se estes apresentam a topografia superficial, a densidade radiográfica e a biocompatibilidade necessária para a continuidade do desenvolvimento deste material. Conforme o exposto em relação ao PPAD, este estudo tem como objetivos:

1. Descrever a topografia superficial de implantes de PPADp e PPADmr por meio de microscopia eletrônica de varredura;
2. Avaliar, por meio de tomografia computadorizada, a densidade radiográfica apresentada pelos implantes de PPADp e PPADmr após sua instalação em calota craniana e tendão dos membros posteriores de coelhos;
3. Descrever o comportamento tecidual dos implantes de PPAD instalados em calota craniana e tendão dos membros posteriores de coelhos por meio da análise histológica em microscopia óptica.

CAPÍTULO 1*

Evaluation of the standard and radiopaque marker high density porous polyethylene by scanning electron microscopy and computed tomography.

Introduction

Alloplastic grafts like the high density porous polyethylene (HDPP) are non-allergenic, non-antigenic, and easy to be shaped[1], do not request a donor site[2] and has a low infection rate[3]. However, it is radiolucent and the visualization of the implant on conventional radiography, computed tomography (CT) or magnetic resonance images is hampered[4-6], specially for postoperative investigation of complications like displacement, extrusion and infection[7] of implants. To improve the postoperative CT visualization, some authors describes modifications of techniques to create an alternative way to indirectly see the HDPP on CT exams, but with reduced effectiveness[2, 8-9]. In order to solve the problem of radiolucency absence, the authors suggested a HDPP associated with radiopaque marker. The aim of this study was to describe the radiolucency features of the 2 new HDPP, standard HDPP (sHDPP) and HDPP with radiopaque marker (rmHDPP), by using tomographic computed (CT) after the application on calvarium and tendon of rabbits in different periods and the micro morphology in scanning electron microscope (SEM).

Materials and methods

This study was approved by the animal research committee of State University of Londrina, protocol n° 30149.2011.67. Were used two kinds of HDPP with 150µm, a sHDPP and rmHDPP (Bismuth Oxide – Bi_2O_3 – in 7% concentration). In order to analyze the superficial morphology of this two different HDPP, 10 specimens of 4.5 X 2 mm were prepared in disk shape (5 sHDPP and 5 rmHDPP) and observed by SEM. The specimens were set with sputter coater of carbon plasma to be analyzed on scanning electron microscope, FEI Quanta 200 (FEI Company, Hillsboro, OR) under 41 and 150 X magnifications.

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* Trabalho formatado conforme normas do *Journal of Craniofacial Surgery* (Anexo A).

To analyze the radiolucency of the HDPP, twenty adults, male, New Zealand rabbits weighed about 3 kg were divided into 4 groups of five animals each. The animals were maintained following *The Canadian Council on Animal Care*[10]*.* Eighty specimens of HDPP was prepared in a disk shape pre-setting 4.5 X 2 mm (40 sHDPP and 40 rmHDPP) and sterilized in ethylene oxide to be implanted. The animals were submitted to surgery under general anesthesia obtained by intramuscular administration of 0.20 mL/Kg of Hydrochloride of Ketamine 1% (Vetbrands, Paulínea, Brazil) associated with 0.15mL/Kg of Hydrochloride of Xylazine 2% (Vetbrands, Paulínea, Brazil). A 10 mm incision was performed on the midline of calvarium to expose both parietal bones. A bone defect was then created on each parietal bone with 4.3mm trephine burs (Neodent, Curitiba, Brazil) 2500 RPM using a counter-angle hand-piece (Kavo, Joinville, Brazil) under constant irrigation with physiological saline solution. On the right parietal bone the rmHDPP were inserted and on left side, the sHDPP; the surgical wound was closed using 5.0 nylon sutures (BRASUTURE, São Sebastião da Gama, Brazil). An second incision was made on both legs to access the tendon of the superior digital flexor muscle; the tendon was longitudinally incised to create a gap to insert the HDPP, in left leg the sHDPP was placed and the right leg the rmHDPP were placed. The wound was closed by suture with 5.0 nylon.

After 7, 14, 45 and 90 post-operative days (periods 1, 2, 3 and 4 respectively), five animals of each group were randomly selected and killed under general anesthesia using a intracardiac lethal injection with 20% of potassium chloride in according with resolution n˚714 of the Brazilian Federal Council of Veterinary Medicine. Parietal bones containing the HDPP were retrieved in blocks and fixed in 10% buffer formalin. The quantitative analysis about Hounsfield Unit (HU) of HDPP was analyzed under computed tomography - CT (BrightSpeed Pro 16 CT, GE Healthcare, WI, USA). The circular region of interest (ROI) tool was used to measure 5.52mm^2. Each ROI were placed under the specimens on the axial plane using a “window implant” with width of 800 and level of 200 setting and measured conform described for visualization of Medpor[9].

Statistical analysis

The data were described as mean and standard deviation (±). To compare the value of HU between sHDPP and rmHDPP in different periods, two-way analysis of variance was used with the *post hoc* Tukey. Moreover, to compare the value of HU between the periods in the same HDPP, one-way analysis of variance was done, also with the *post hoc* Tukey. Statistical significance was set at $p < 0.05$.

Results

Under SEM analysis, the sHDPP and rmHDPP specimens did not show significant morphological difference at 41 and 150X magnification (figure 1), except for presence of the crystals on the superficies of the specimens with radiopaque marker which was clearly identified on large magnifications (figure 2). The distance between the pores were variable in both HDPP specimen, ranging from 136.43 to 426.53µm.

A total of 80 HDPP *in vivo* samples were analyzed under CT. The sHDPP and rmHDPP showed different density radiographic (figure 3). The values of HU of rmHDPP were higher than sHDPP in all periods on both sites (p<0.001 for all) (table 1 and 2). When the values of the HU of rmHDPP were analyzed, comparing the periods only on bone tissue, were found different values between all periods (p<0.03), except between the periods 2 and 3 (p=0.05). In tendon tissue, the rmHDPP presented different values between the periods 1 and 3 (p<0.001), 1 and 4 (p=0.001), 2 and 3 (p=0.002) and 2 and 4 (p=0.02). The analysis of sHDPP on bone tissue, showed difference between periods 2 and 4 (p=0.02), while on the tendon tissue there was no difference between periods (figure 4).

Discussion

The necessities to create a new material or modify consolidated materials are frequently found on literature[11-15] and that purpose is focused to improve some deficiency. The HDPP has been widely used in facial reconstruction for over 25 years and at this moment, the available HDPP shows the same features[9, 16-18]. Focused on material improvement, we had inserted HDPP associated with a radiopaque marker, the bismuth oxide; that radiopacifier have been used in endodontic cement materials[19-21]. Our results showed that although the rmHDPP could be visible on CT, this material suffered decrease of HU during the assay, what suggest that radiopacifier stability still a problem. Regarding the sHDPP, that showed slight increase in HU value during the periods similar to the results found by Vendemia *et al*[9]. We believe that values of HU were increased because the ingrowth of tissue among the pores according to Klawitter *et al.*[22], and this tissue promoted the different value on sHDPP.

Concerning the morphological analyses performed in SEM, there was no literature available about this specific analysis on HDPP, except some studies that showed a few images of SEM[4, 23-25], but without a precise morphological analysis; those studies were very similar to the image obtained in the present study. The size of pores was similar to that of MEDPOR®, which was described in many studies with minimum pores size of 150µm, a minimum value accepted to promote ingrowth of soft tissue into pores[26-30]. In our study, both specimens showed the same morphological characteristics, except for the presence of crystals on the surface. Detachment of these crystals could explain the reduction of HU on CT analysis. Another test should be performed to describe what happened with this specific material.

Regardless of limitation on rmHDPP, the sHDPP specimen showed good results and this encouraged us to find a way to improve this problem and probably make other studies with the rmHDPP.

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Figure 1 - sHDPP (A) and rmHDPP (C) under magnification of 41X; sHDPP (B) and rmHDPP (D) under magnification of 150X.

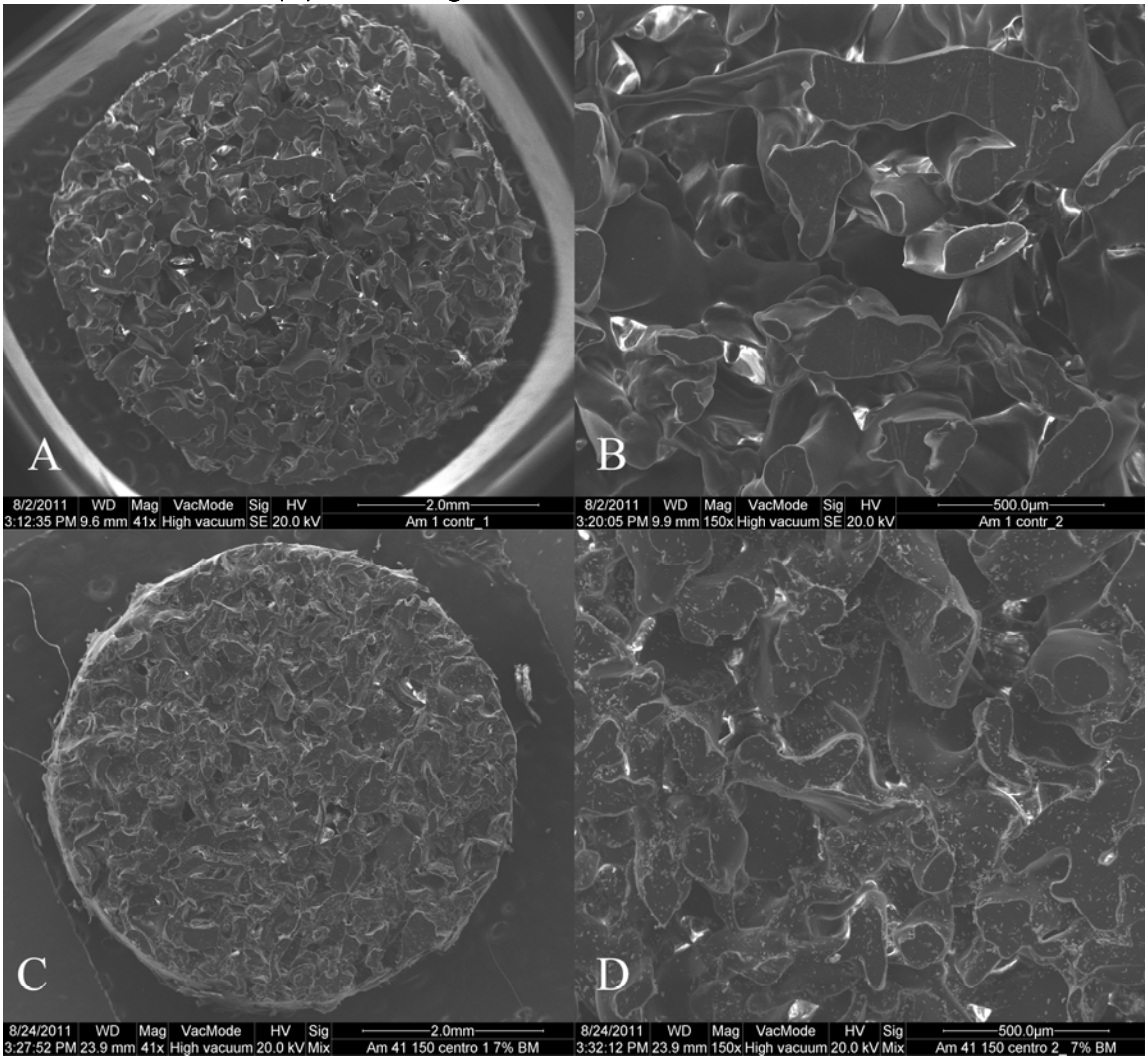


Figure 2 - rmHDPP showing the interpores space with bismuth oxide crystals (arrows) under 2800X (A) and 6000X (B) magnification.

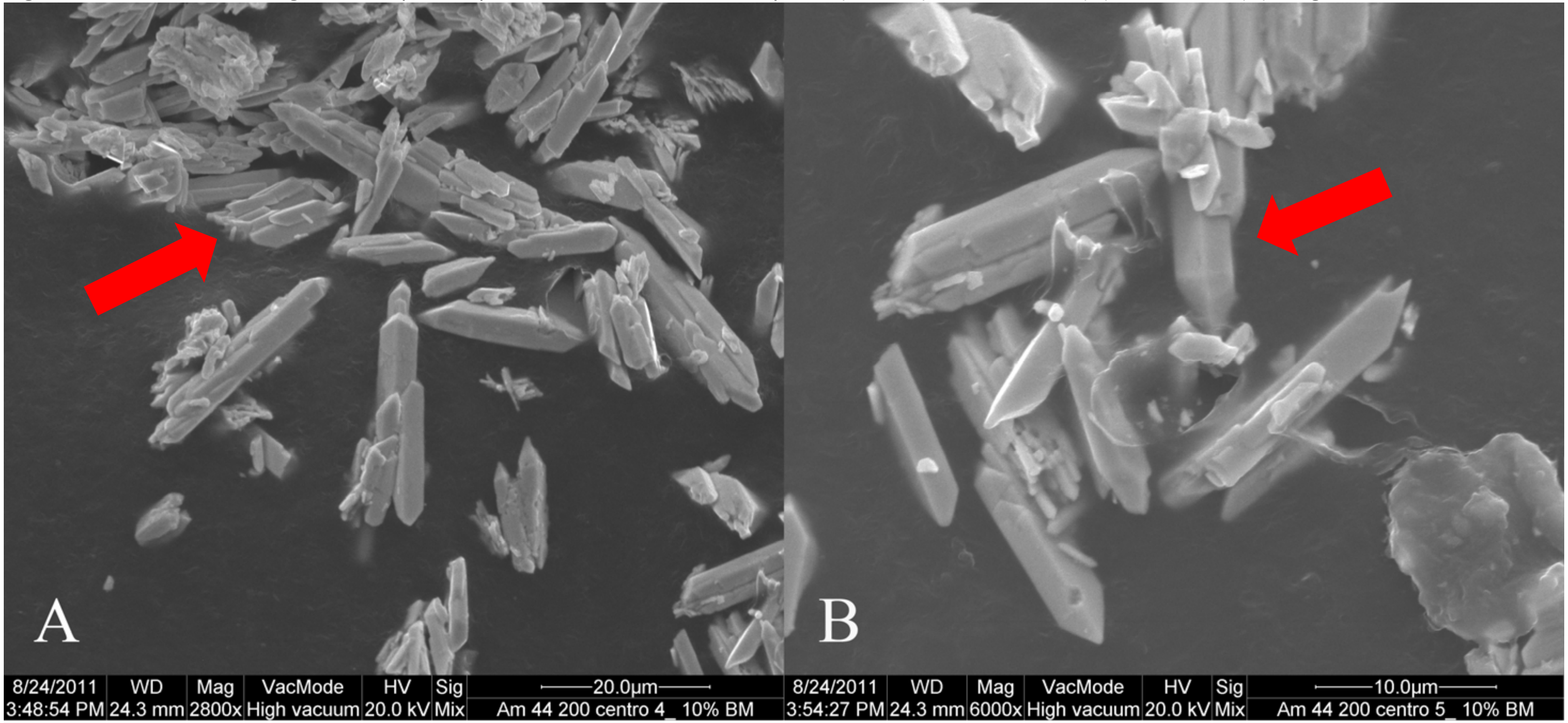


Figure 3 - (A) Axial and coronal images of the calvarium under computed tomography showing the hyper density different between sHDPP and rmHDPP (arrows). (B) 3D reconstruction showing upper and posterior view of the same specimens.

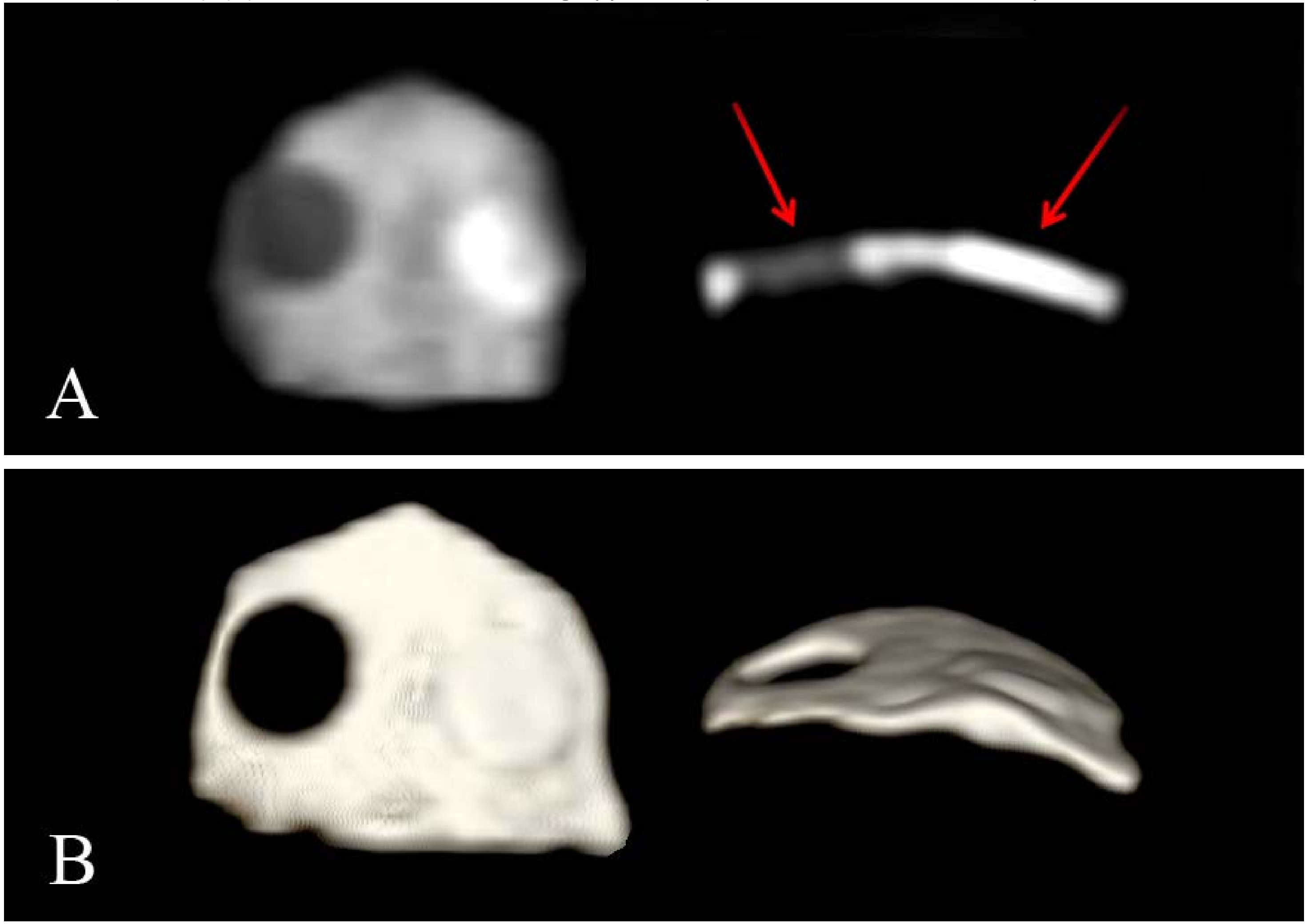


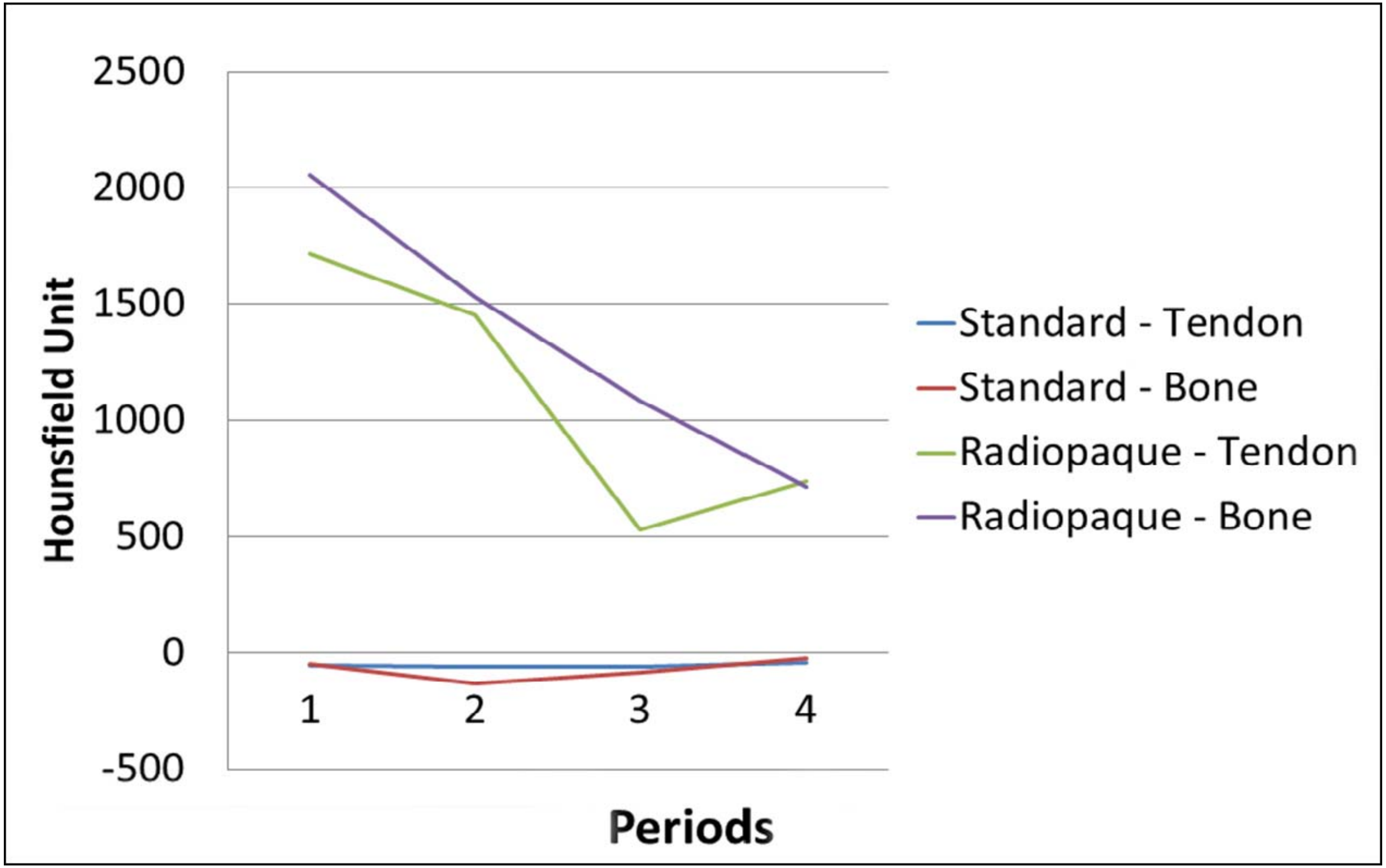
Table 1 - Values (mean) in Hounsfield Unit of rmHDPP and sHDPP in different periods on bone tissue.

Tissue	Kind of HDPP	Values HU in Periods			
		1	2	3	4
BONE	rmHDPP	81,5	-130,7	-84,5	22,3
	sHDPP	2058,4	1531,9	1089,2	717,7
TENDON	rmHDPP	-55	-61,4	-58,5	-42,2
	sHDPP	1719	1453,6	528,1	737,7

Table 2 - Comparison between rmHDPP and sHDPP in different periods on tendon and bone tissue.

Tissue	Kind of HDPP	Periods
BONE	rmHDPP	1 ≠ 2 = 3 ≠ 4
	sHDPP	1 = 3 = 2 ≠ 4
TENDON	rmHDPP	1 = 2 ≠ 3 = 4
	sHDPP	1 = 2 = 3 = 4

Figure 4 - Representation of mean in different periods, tissue and kind of HDPP.



CAPÍTULO 2[‡]

Evaluation of the biocompatibility of two kinds of high-density porous polyethylene implants.

Introduction

Biomaterials or bioactive implants are materials that have a good interaction with organic tissues, are non-antigenic, infection resistant and frequently promote tissue ingrowth allowing the biological bonding of the implant[1, 2]. Nowadays, biomaterials are widely used in medicine and have different origins such as metals, polymers, ceramic and glasses[3] and are represented by a large spectrum of materials like silicone, polyethylene, expanded polytetrafluoroethylene, acrylic polymers, bioactive glasses, hydroxyapatite and carbonate and calcium phosphates[2]. Several biomaterials are availability in craniofacial surgery, each of them with a specific application. Despite those options, autogenous bone grafts are still considered the gold standard[4]. Nevertheless, in specific situation, when the use of autogenous bone grafts is not convenient or unavailable, the synthetic biomaterials can be used. The high-density porous polyethylene (HDPP) is considered a good option because of their proprieties to be easily shaped, no degradable and tissue growth inside the pores[5-8]. HDPP has been extensively used to promote facial contour recovery in esthetic surgery[2,9], treatment of sequelae in ablative facial surgery[10], recovery of anatomic after craniofacial trauma[11] and replacement of the ocular globe volume after ocular enucleation or evisceration[12, 13]. Although of these use indications, HDPP is indicated when the surgical site that allows adequate stabilization to avoid dislocation and/or contamination of the implant[14]. The aim of this study was to evaluate the tissue reaction of two HDPP types: standard (sHDPP) and with radiopaque marker (rmHDPP), both commercially unavailable yet, on calvarium bone and tendon in an animal model by means of descriptive histological analysis.

[‡] Trabalho formatado conforme normas do *Journal of Craniofacial Surgery* (Anexo A).

Materials and methods

This study was previously assessed and approved by Animal Committee of State University of Londrina protocol n˚ 30149.2011.67. It was used twenty New Zealand rabbits, male, weighing of approximately 3 kg that were maintained following *The Canadian Council on Animal Care*[15]. These animals were divided 4 groups with five animals each, conform the sacrifice periods. The HDPP were prepared using two kinds of the HDPP with 150µm, a sHDPP and rmHDPP (Bismuth Oxide – Bi_2O_3 – in 7% concentration), in a round shape pre-setting 4.5X2mm and sterilized in ethylene oxide to be implanted. The animals were submitted to surgery under general anesthesia by intramuscular administration of 0.20 mL/Kg of Hydrochloride of Ketamine 1% (Vetbrands, Paulínea, Brazil) associated with 0.15mL/Kg of Hydrochloride of Xylazine 2% (Vetbrands, Paulínea, Brazil). A 10 mm skin incision was performed on the calvarium sagittal midline to expose both parietal bones. After this, a defect bone in each side was created with trephine burs 4.3mm (Neodent, Curitiba, Brazil) 2500 RPM mounted in contra-angle hand-piece (Kavo, Joinville, Brazil) under constant irrigation with saline physiological solution. On right parietal bone it was implanted the rmHDPP and on the left side the sHDPP; the surgical site was closed using a 5.0 nylon suture (BRASUTURE, São Sebastião da Gama, Brazil).

Another incision was made on both legs to access the superficial digital flexor muscle tendon. It was incised to create a gap to insert the rmHDPP on right side and the sHDPP on left side; the specimens were stabilized by suture with 5.0 nylon. Postoperatively the animals received a solution of piroxicam and penicillin 8.000UI/Kg (MSD saúde animal, Cruzeiro, Brazil). Throughout the post-operative period the animals were followed by a veterinarian, and complications or behavioral changes weren't observed on trans or post-operative period, returning to their normal diet and did not show weight loss during all the time of this study.

After 7, 14, 45 and 90 days post-operative, five animals from each group were selected and killed by intracardiac lethal injection with 20% of potassium chloride under general anesthesia in according with resolution n˚714 of Brazilian Federal Council of Veterinary Medicine. The HDPP was retrieved in blocks and fixed in 10% buffer formalin and the blocks with bone were decalcified in a electrolyze machine in 4% EDTA solution. Transversal histologic slices were obtained and stained with hematoxilyn-eosin.

Results

Bone Analyses

On histological analysis, the rmHDPP and sHDPP inserted on bone showed the same pattern of connective tissue infiltration on interglobular space and interface. At the first dead period, the connective tissue was immature, while in 14 days the tissue was a slight more organized with presence of neutrophils, fibroblasts and blood vessels (figure 1). At 45 days, both kinds of HDPP showed tissue with mature aspect with blood vessels with hemaciae into and fibroblast collagen fibrous around (figure 2). A different finding was the presence of radiopaque marker spread throughout the tissue and not only restricted to the specimens (Figure 3). In 90 days, there were no differences between the rmHDPP and the sHDPP, where both of them showed small focal bone formation and the presence of cartilaginous tissue (figure 4).

Tendon Analyses

There was no histological difference between the rmHDPP and sHDPP on tendon at all periods analyzed. At 7 days both types of HDPP showed an ingrowth of connective tissue on interface and intergranular spaces (figure 5). In 14 days, there was augmented presence of blood vessels, while in 45 and 90 days there is the same model of cell presence (figure 6) except of presence of supernatant radiopaque marker found in 45 days.

Discussion

Several biomaterials are available to use in craniofacial surgery, one of them is the HDPP. This biomaterial is made from synthetic, high-density polyethylene powder that is strong yet flexible and easily molded into shapes[13] and the use of HDDP is widely because of its good biological features (infection resistance, no antigenic and promotes tissue ingrowth)[1, 5]. Improve a consolidated material is a challenge to all researchers, to try this, our lab modified the sHDPP eith radiopaque marker. We know that the polyethylene is a gold standard biomaterial to research and many others materials have been tested together[16-19], and several studies on literature have shown biocompatibility like the HDPP tested [12, 15, 20-22]. Others authors have described that the HDPP in animals models shows fibrovascularization with ingrowth of viable vascular connective tissue occurring in 4 weeks[23-25], as the results found in our study, as well as the presence of bone neoformation while the HDPP was in contact with bone tissue. This bone neoformation was previously cited by Oliveira *et al.*, 2009[15] that describes a lamellar mature bone inside the pores in 90 days and also warns that the HDPP is not an osteinductive material but it has an appropriate architecture to tissue ingrowth; despite this information, the neoformation bone no was found when the HDPP is used in human, conform Tark *et al,* 2012[21], indicating that the HDPP have not osteogenic effect through osteoconductive activity in humans. This is an important information when of the use in humans.

The development of new biomaterials should be focused on production of the materials that enhance on short-term the wound healing, the stability and consequently the follow-up[2]. The use of composited materials to enhance the application and healing is common in medicine[26, 27]. The uses of bismuth oxide concomitant with other biomaterials are safety and frequently found on dental materials[28-30]. The HDPP associated with bismuth oxide, a radiopaque marker, is a kind of composite that improves the radiographic follow-up because can be visualized in conventional radiographic and computed tomographic exams. The necessities of radiographic follow-up in conventional HDPP have been described[7, 31] and this is important to clinical evaluation. Anyway, despite of our modification being created with the purpose of being visualized on image exam and this HDPP shows an instable bond between bismuth oxide crystals and the surface of HDPP, this problem was visualized after 45 days in both tissue, the HDPP with supernatant bismuth oxide were found on histological slice and did not show any inflammation process. Probably this detachment occurred on histological preparation, but if this radiopaque marker was not bond tightly with HDPP, perhaps this kind of radiopaque marker should not be used for this propose.

The availability of the biomaterial is growing as well as its use. Several biomaterials promise goods results, but they are not always reached and this is a jeopardizes on applicability and consequently the clinical evaluation. All new biomaterials should be regarded with suspicion until occur the counterproof. The two HDPP that were tested showed adequate biocompatible results; the composite of rmHDPP although having also showed goods results, had cleavage of bismuth oxide bond with of the HDDP. Thereby, further research should be done to improve the manufacturing of this kind of HDPP.

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Figure 1 - 14 days infiltrated connective tissue under interglobular spaces in rmHDPP and the radiopaque marker crystal (A - arrow) and sHDPP (B). 20X magnifications.

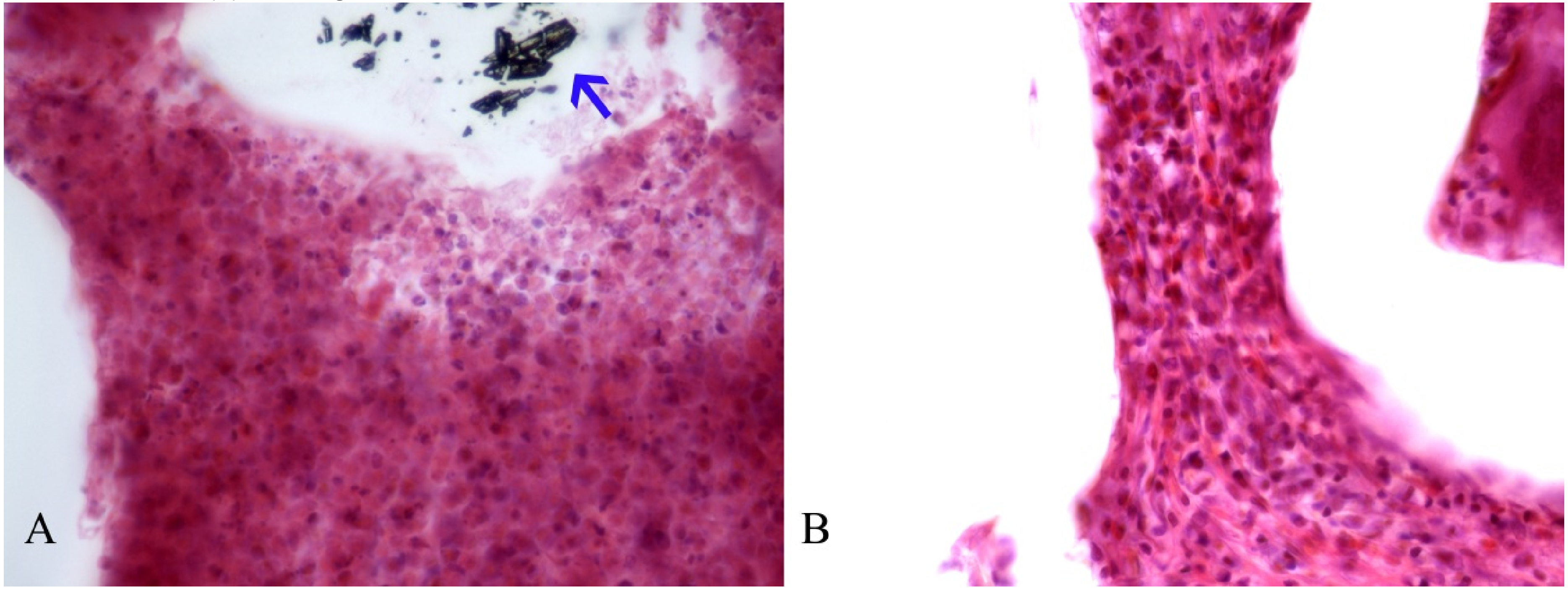


Figure 2 - Magnification of 40X. 45 day infiltrated connective tissue with fibroblasts, blood vessel and hemaciae (arrow).

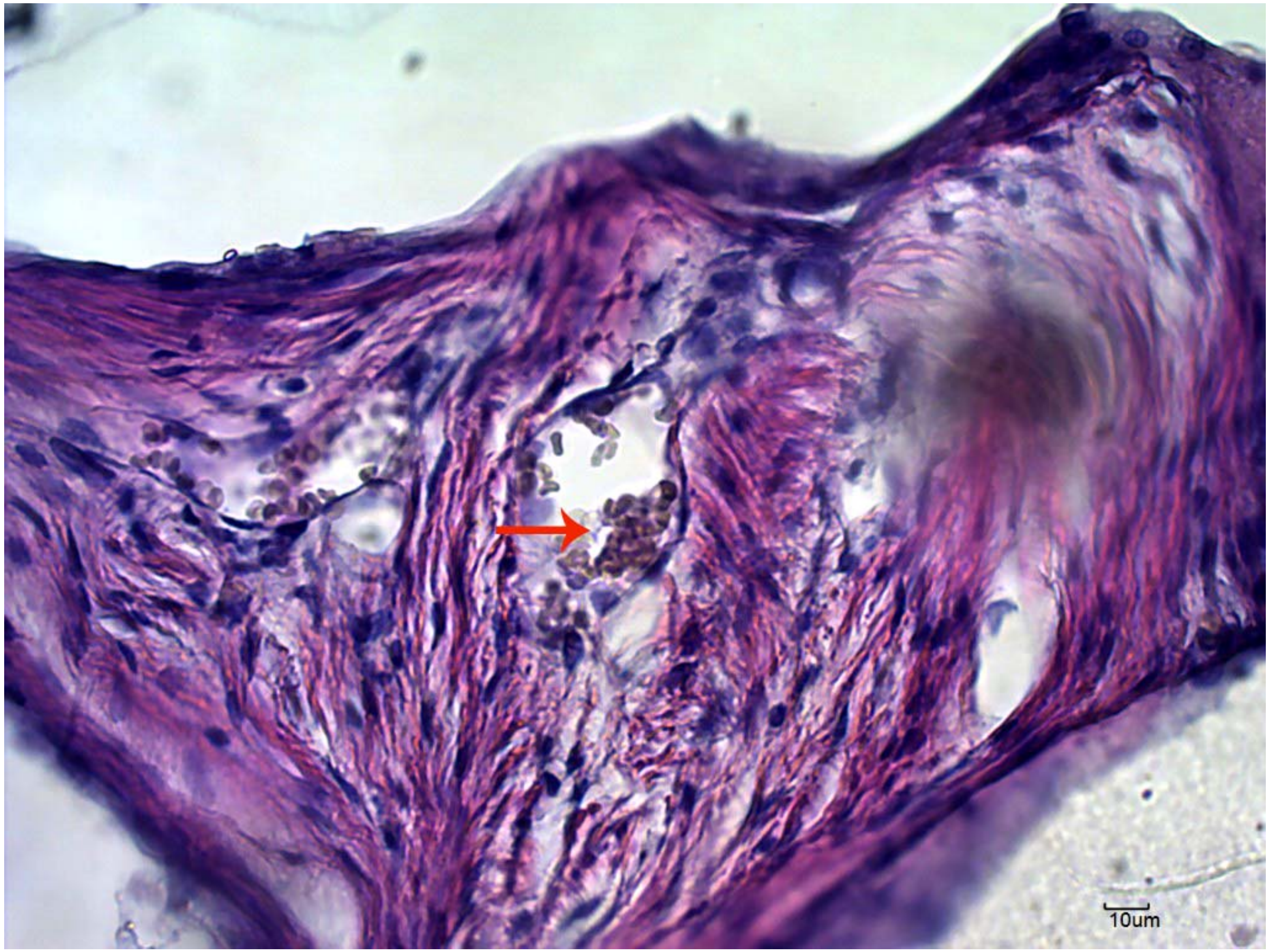


Figure 3 - Radiopaque marker supernatant was viewed on 45 days. Arrows identified on view of 5X (A) and 40X magnification (B).

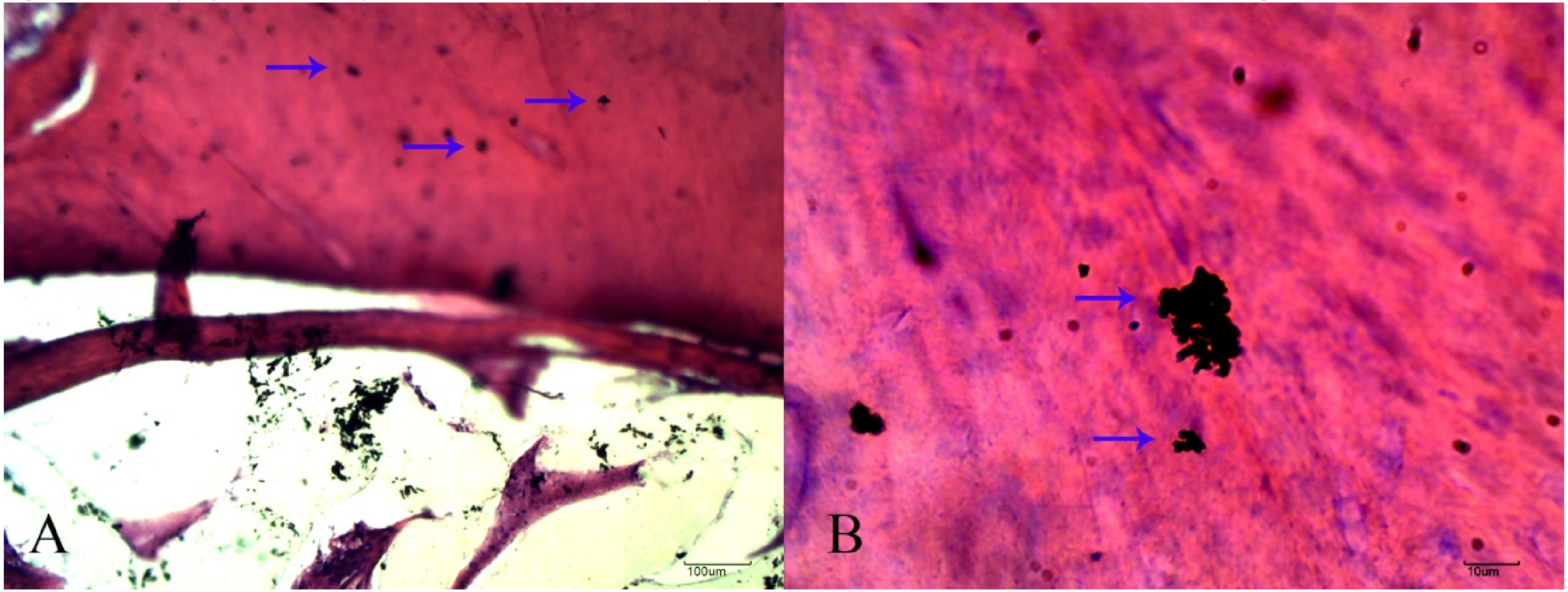


Figure 4 - 90 days with interglobular space showed small focal bone formation (A – 5X magnification). Bone (arrows) and cartilaginous (*) tissue are clearly identified on 20X magnification(B).

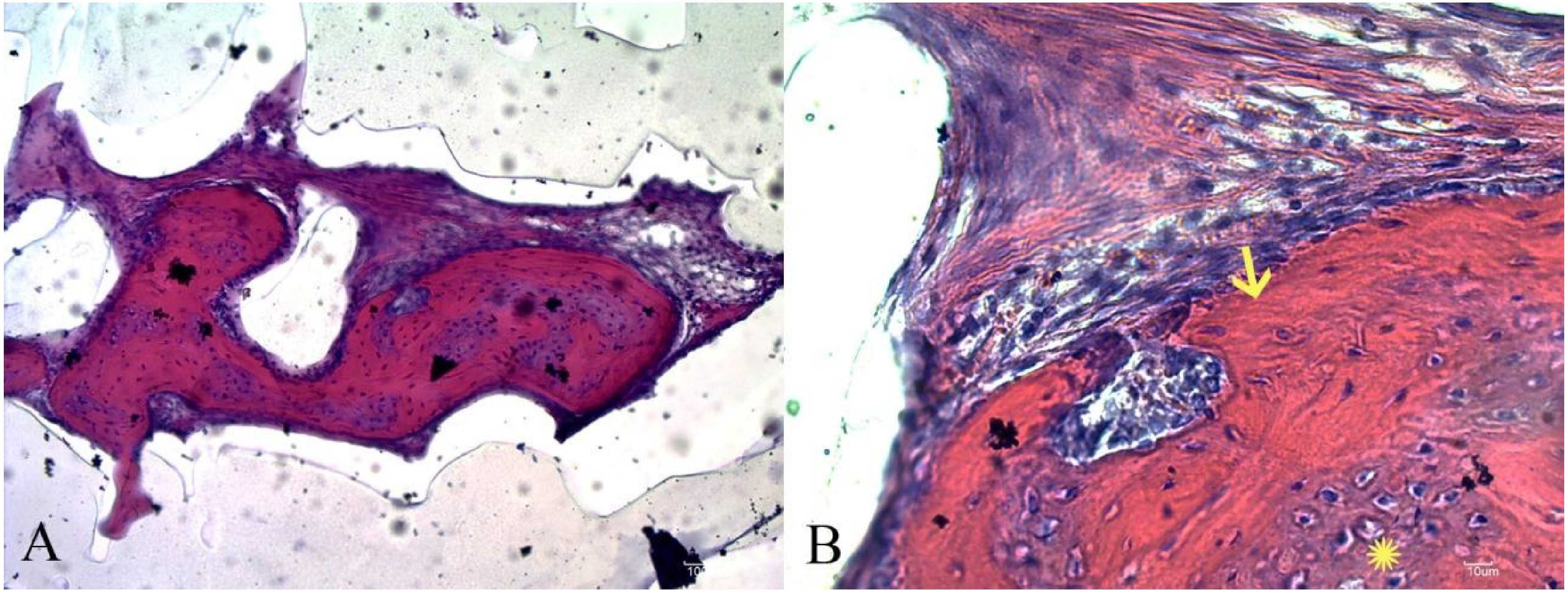


Figure 5 - 7 days and 5X magnification. Same pattern of ingrowth connective tissue in rmHDPP (A) and sHDPP (B)

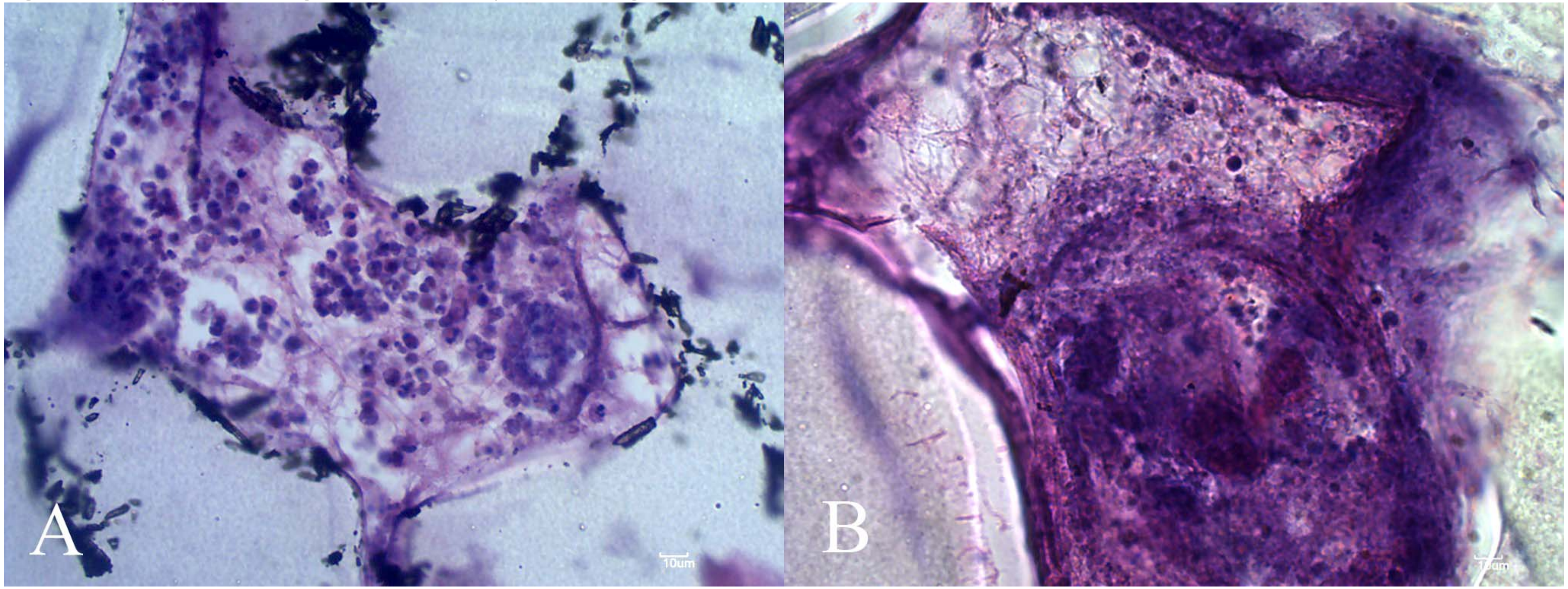
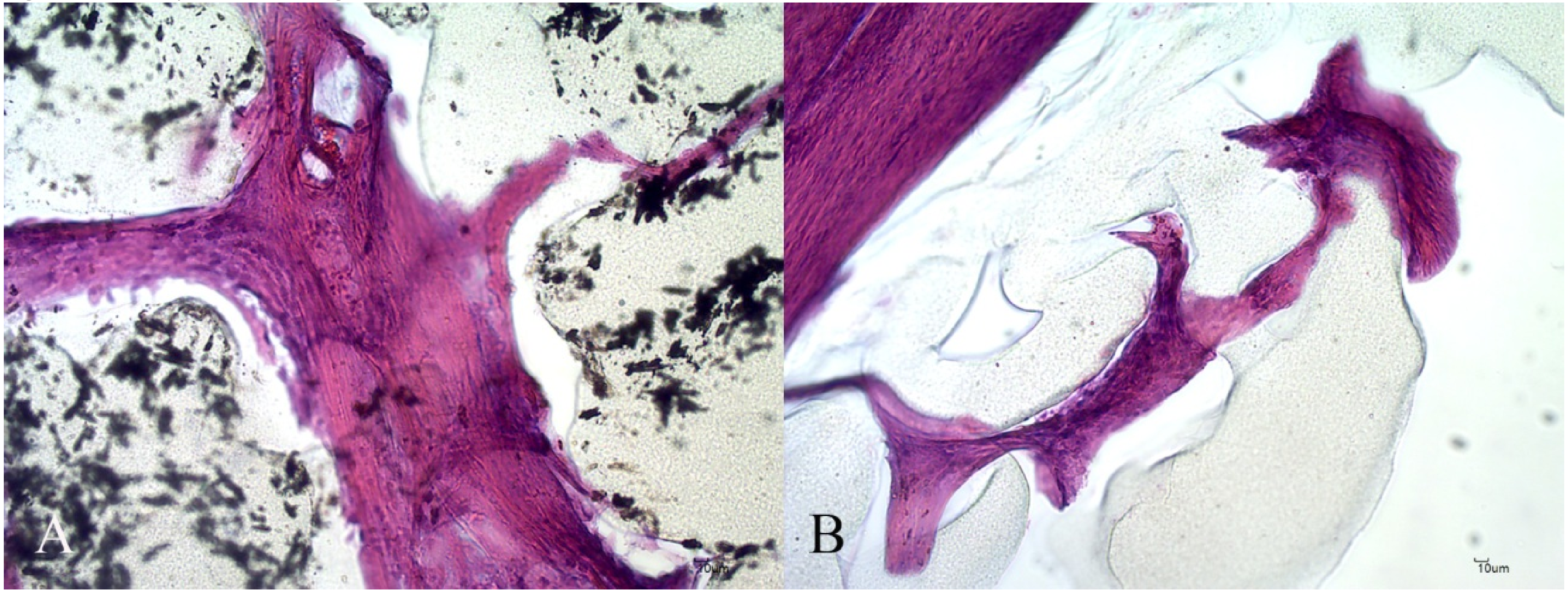


Figure 6 - 90 days and 20X magnification. Mature connective tissue on rmHDPP (A) and sHDPP (B).



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GLOSSÁRIO

- µm: micrometro;
- *Computed Tomography (CT)*: Tomografia computadorizada;
- *Expanded polytetrafluoroethylene/ePTFE*: politetrafluoretileno expandido;
- *Fan Beam*: tipo de tomógrafo computadorizado que utiliza colimador de raio-x com feixe em leque;
- *High-density porous polyethylene with radiopaque marker* (*rmHDPP):* polietileno poroso de alta densidade com marcador radiopaco;
- *Hounsfield Unit (HU)*: Unidade de Hounsfield – unidade de absorção de radiação pelos tecidos irradiados;
- Implantes aloplástico / *alloplastic grafts*: implante que molda ou passível de ser moldado;
- *In vitro:* palavra originária do Latim ("em vidro") que refere-se a experimentação feita fora do organismo em ambiente controlado associado ao laboratório;
- *In vivo:* palavra originária do Latim ("em vivo") que refere-se a experimentação feita dentro ou no tecido vivo de um organismo;
- Kg: quilograma;
- mL: mililitro;
- mm: milímetro;
- mm^2: milímetro quadrado;
- PPAD / *HDPP*: Polietileno poroso de alta densidade / *High density porous polyethylene*;
- PPADmr: polietileno poroso de alta densidade com marcador radiopaco;
- PPADp: Polietileno poroso de alta densidade padrão;
- *Region of interest (ROI)*: Região de interesse – ferramenta utilizada em *workstation* para avaliação da unidade Hounsfield em determinada região do exame tomográfico;
- *Scanning electron microscope (SEM)*: Microscópio eletrônico de varredura;
- *Standard high-density porous polyethylene (sHDPP)*: polietileno poroso de alta densidade padrão;
- *Value p*: nível de significância estatística;
- *Workstation*: estação de trabalho utilizada em aparelhos de tomografia computadorizada.

ANEXOS

ANEXO A

Normas de publicação da revista *Journal of Craniofacial Surgery* a qual será submetido os capítulos 1 e 2 desta dissertação.

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The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

Unstructured abstract and key words: Limit the abstract to 250 words. It must be factual and comprehensive. Limit the use of abbreviations and acronyms, and avoid general statements (eg, "the significance of the results is discussed"). List three to five key words or phrases.

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Abbreviations: For a list of standard abbreviations, consult the **Council of Biology Editors Style Guide** (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

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Journal article

1. Farkas LG, Tompson B, Phillips JH, et al. Comparison of anthropometric and cephalometric measurements of the adult face. *J Craniofacial Surg*1999;10:18-25

Book chapter

2. Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J. eds. *Frames of Reference for Pediatric Occupational Therapy*. Philadelphia: Lippincott Williams & Wilkins, 1999:205-256

Entire book

3. Kellman RM, Marentette LJ. *Atlas of Craniomaxillofacial Fixation*. Philadelphia: Lippincott Williams & Wilkins 1999

Software

4. **Epi Info** [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention; 1994

Online journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22-37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996

World Wide Web

7. Gostin LO. Drug use and HIV/AIDS [**JAMA** HIV/AIDS web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997

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ANEXO B

Parecer do Comitê de ética no uso de

animais

Universidade
Estadual de Londrina

COMISSÃO DE ÉTICA NO USO DE ANIMAIS

OF. CIRC. CEUA Nº 113/12

Londrina, 13 de Abril de 2012.

Prezada Pesquisadora,

O CEUA/UEL, reunido em 10 de abril de 2012, avaliou o projeto de pesquisa intitulado **"Avaliação da biocampatibilidade de um polietileno poroso de alta densidade de fabricação nacional."**, registrado sob o processo nº 30149.2011.67, pesquisa da Clínica odontológica universitária, desenvolvido sob sua responsabilidade, julgando-o como ***aprovado*** para execução entendendo-se que os princípios éticos postulados pelo Colégio Brasileiro de Experimentação Animal e Conselho Nacional de Controle de Experimentação Animal estão respeitados.

Serão utilizados 16 coelhos da espécie *Oryctolagus cuniculus* machos com peso de 3,5 – 4,0 kg, distribuídos em 4 grupos de 4 animais, adquiridos pelo centro de criação da Universidade Estadual de Maringá. Neste projeto será avaliada a biocompatibilidade de um novo PPAD por meio de análise histológica das reações teciduais após a inserção de corpos de prova do material em tendão do membro posterior direito e intraósseo na calota craniana nos coelhos. Para isto os coelhos serão anestesiados com quetamina e xylazina, será realizada uma incisão na pele, expondo o tendão do músculo flexor digital superficial onde será fixado o corpo de prova, após a inserção do PPAD, a incisão será fechada. Posteriormente será realizado o acesso cirúrgico na calota craniana, qual será feito uma osteotomia do osso parietal e removido o bloco ósseo e no mesmo local inserido um disco de PPAD para preenchimento, e fechamento da incisão Os animais receberão Pencivet PPU como protocolo antimicrobiano, e o Cloridrato de Tramadol nos 3 primeiros dias de pós-operatório para alívio da dor. Os coelhos serão submetidos à eutanásia em dias diferentes após a cirurgia e as áreas contendo implantes de PPAD serão excisadas e fixadas em formol para confecção de laminas e análise histológica para avaliação de fibrovascularização, osteogênese e inflamação. Como será realizado monitoramento diário dos animais, recomendamos que caso existam sinais sugestivos de dor além do período de 3 dias seja realizado tratamento com os analgésicos mencionados acima. Os experimentos estão previstos para serem desenvolvidos em 24 meses após sua aprovação no CEUA-UEL.

Cumpre orientar que caso pretendam-se quaisquer alterações no protocolo experimental aprovado, deve-se submeter o novo protocolo à apreciação do CEUA/UEL anteriormente à execução das modificações.

Sem mais para o momento, subscrevo-me. Cordialmente,

Waldiceu Ap. Verri Junior
Prof. Dr. Waldiceu Aparecido Verri Junior
Coordenador da CEUA/UEL

Ilmo. Sr
Prof. Dr Glaykon Alex Vitti Stabile
Coordenador do Projeto
Departamento de Clínica Odontológica Universitária
Centro de Ciências da Saúde
Com cópia para Srª Égle Maria de Sousa (Chefe da DCA/PROPPG)

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